Review of Necrotizing Enterocolitis and Spontaneous Intestinal Perforation Clinical Presentation, Treatment, and Outcomes

Laura A. Rausch, MD, MPH, MA[a,b,c], David N. Hanna, MD[a], Anuradha Patel, MD[d], Martin L. Blakely, MD, MS[d,*]

KEYWORDS

• Necrotizing enterocolitis • Spontaneous intestinal perforation • Toll-like receptor 4 • Nitric oxide synthase • Cerebral palsy

KEY POINTS

- Surgeons should make deliberate attempts to distinguish NEC and SIP when considering surgical treatment options.
- Use of ultrasound to inform surgical treatment requires further study.
- With presumed NEC, initial laparotomy likely leads to lower rates of death and neurodevelopmental impairment.

INTRODUCTION

Necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) are 2 neonatal conditions that have been widely investigated but continue to have frequent morbidity and high mortality. In this review, we will discuss the differences and similarities in clinical presentation, pathophysiology, treatment, and outcomes for NEC and SIP. NEC effects 2% to 9% of preterm neonates, and nearly 10% of preterm infants with very low birthweight (VLBW, <1500 grams).[1,2] The mortality rate of extremely low birth weight (ELBW, <1000 grams) neonates is 30% to 50% and for VLBW neonates ranges from 10% to 30%. There is variation in incidence of disease based on gestational age (GA), birthweight, country of origin, with the lowest reported

[a] Vanderbilt University Medical Center, 2200 Children's Way, Suite 7100, Nashville, TN 37232, USA; [b] Vanderbilt University Master of Public Health School, 2200 Children's Way, Suite 7100, Nashville, TN 37232, USA; [c] Geriatric Research Education and Clinical Center, 2200 Children's Way, Suite 7100, Nashville, TN 37232, USA; [d] Monroe Carell Jr. Children's Hospital at Vanderbilt, 2200 Children's Way, Suite 7100, Nashville, TN 37232, USA
* Corresponding author.
E-mail address: martin.blakely@vumc.org

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incidence in Japan (2%) and the highest in Australia, Canada, and Italy ranging from 7% to 9% of preterm infants. This variation in incidence rates among countries[1,2] suggests that there are various factors influencing the development of NEC including environment, diet, and genetic predisposition.[1]

Over the years, there have been increasing reports of SIP in VLBW and ELBW neonates. For neonates with a GA less than 32 weeks, the reported incidence rate was 1.6% based on National Inpatient Sample dataset from 2002 to 2017. This cohort demonstrated increased incidence of SIP with decreasing GA. In the cohort, 90% of cases were less than or equal to 28-week GA, with 82% of the neonates being ELBW and more prevalent in male versus female neonates.[3] The incidence rates of NEC and SIP change over time, and ongoing study is important.

CLINICAL PRESENTATION

NEC and SIP are 2 intra-abdominal conditions that have significant overlap in clinical presentation. The optimal treatment modality of these 2 distinct disorders likely differs; therefore it is important for clinicians to distinguish between NEC and SIP before initiating the surgical treatment. NEC is thought to be primarily driven by ischemia and initiation of enteral feeds resulting in full-thickness hemorrhagic necrosis. SIP is localized to the area of perforation and is characterized as isolated mucosal ulceration with submucosal thinning.[4,5] Thus, SIP can occur before the initiation of enteral feeds in LBW and ELBW infants.[6,7] In SIP, operative findings typically involve a single subcentimeter perforation, usually on the antimesenteric border of the small intestine with minimal peritoneal contamination and healthy appearing surrounding intestine.[5] Although a perforation is often present in NEC, the surrounding bowel is not typically healthy-appearing and requires a small bowel resection with or without stoma creation.

A particular challenge in differentiating NEC from SIP is that the definition of NEC has evolved during the last several decades. Scoring systems, such as Bell's criteria and the modified Bell's criteria, have primarily served to communicate severity of disease, rather than specifically diagnose NEC from other forms of gastrointestinal illness.[8] More recent attempts to standardize the definition of NEC, including the Stanford NEC score, the International Neonatal Consortium NEC workgroup definition, and the Centers for Disease Control and Prevention definition, incorporate laboratory and radiographic signs that help limit and objectify the definition of NEC.[9–11] However, such definitions and scoring systems are seldom used by clinicians at the bedside when evaluating a neonate with symptoms typical of NEC or SIP. Thus, clinicians should consider risk factors, physical examination findings, radiographic findings, and specific laboratory markers that are specific to NEC or SIP.

No maternal characteristics, such as age, parity, multiple gestations, or mode of delivery, have been implicated in NEC or SIP, and there is significant overlap in the clinical presentation of infants with NEC and SIP.[4,6] Infants with either disorder may develop bloody stools, abdominal distension, and may have an accompanying bilious output from a nasogastric decompression tube. However, infants with SIP consistently develop a bluish discoloration of the abdomen, which is a hallmark differentiator from NEC.[5,12–15]

There are multiple risk factors that are associated with the development of NEC. The following are consistently described: formula feeding, intestinal dysbiosis, low birthweight, and prematurity.[1,16] It has also been reported with acid-suppressing medications, acute hypoxia, antibiotic exposure, blood transfusions, cardiac anomalies, neonatal anemia, and mechanical ventilation.[2,17] Prematurity is the only well-

established risk factor for SIP, although there are other antenatal and prenatal risk factors based on limited data from case series, for which a conclusive association has not been established.[10]

IMAGING

The diagnosis of NEC or SIP is supported by standard imaging modalities, such as abdominal X-rays and ultrasound. Abdominal X-rays (supine and lateral) may provide findings that can help the clinician differentiate between NEC and SIP. Although pneumoperitoneum occurs in both entities, neonates with NEC may demonstrate significant bowel distension or fixed bowel loops, whereas neonates with SIP are likely to demonstrate a paucity of bowel gas or a gasless abdomen.[18] Abdominal ultrasound may provide other specific signs of NEC, such as thickened intestinal walls, pneumatosis intestinalis, and portal venous gas. Ultrasound has been shown to be a valuable tool in differentiating NEC from SIP. Several early studies demonstrated portal venous gas to be a highly sensitive and specific sign of NEC, and more recent studies have demonstrated its high specificity.[19–23] Additionally, ultrasound may demonstrate a localized area of peritoneal contamination that may direct peritoneal drain placement should the clinician elect to place one, although this is not used commonly. There are no large, multicenter studies clearly documenting the added value of ultrasound in the diagnostic distinction of NEC and SIP or in the management of these conditions, and this is an important area where further study is needed. It likely can play an important role but reliable supporting evidence is in the early phases.

PATHOPHYSIOLOGY

The pathophysiology of NEC is multifactorial, and there is active ongoing research to determine factors and processes that lead to this devastating disease. The time from birth to the onset of NEC is inversely proportional to GA,[10] with the more premature infants developing NEC at a later postnatal age and less preterm infant developing it sooner after birth. The development of NEC seems to reach a peak around 29 to 32 weeks postmenstrual age.[16] The classic pathophysiology understanding is that intraluminal bacteria disrupt and invade intestinal epithelium at the tip of the intestinal villi. This then leads to the endotoxin from the bacteria to bind to the toll-like receptor 4 (TLR4) on intestinal epithelial cells, leading to the activation of the pathogen-associated molecular pattern receptors. This ultimately leads to break down of gut barrier and allows bacteria to translocate inciting an inflammatory response in lamina propria led by TNF-alpha, IL-1beta, and other cytokines. The activation of complement and coagulation systems causes leukocytes and platelets adherence to the endothelium, thereby decreasing blood flow in microvasculature and causing tissue injury leading to coagulative necrosis and sepsis.[1] Currently, there are multiple potential mechanisms that have been extensively researched and currently investigated, including the role of TLR4 and nitric oxide, disruption of microvascular blood flow (intestinal ischemia), the effect of dysbiosis, and the reduced activity of intestinal stem cells.[1,4–7]

The cause of SIP largely remains unknown, with several cases reporting thinning or absence of muscularis propria at the site of perforation.[5] One mechanism regarding the role for abnormal or delayed nitric oxide synthase (NOS) has been hypothesized, this is based on single study of NOS knock out mouse model that demonstrated ileal perforation with exposure to indomethacin and/or dexamethasone.[24] The following processes have been demonstrated to be upregulated in SIP but milder in samples taken from patients with SIP compared with those with NEC: changes in

immunoregulatory pathways regarding angiogenesis, arginine metabolism, cell adhesion and chemotaxis, extracellular matrix remodeling, hypoxia and oxidative stress, inflammation, and muscle contraction.[25,26]

TREATMENT OF SURGICAL NECROTIZING ENTEROCOLITIS AND SPONTANEOUS INTESTINAL PERFORATION

There are promising signs that the incidence of NEC is decreasing over time but until this devastating disease of prematurity can be reliably prevented, it is incumbent on pediatric surgeons and neonatologists to study outcomes with currently available surgical treatments with the goal of optimizing outcomes.[27] Unlike many other neonatal surgical therapies, which typically are "understudied," there have now been 3 randomized clinical trials (RCT) comparing laparotomy versus peritoneal drainage at disease onset. Questions remain but there is reliable evidence for pediatric surgeons and neonatologists to now use in their clinical decision-making and to use in discussions with parents of infants with these conditions.

The first 2 RCTs compared initial laparotomy versus peritoneal drainage in different populations of infants with surgical NEC or SIP and each of these primarily evaluated mortality rates.[28,29] The NEC Steps trial was an important RCT within pediatric surgery, being one of the very few multicenter RCTs supported by National Institutes of Health (NIH) funding. This trial enrolled 117 infants up to 1500 grams birthweight and found that there was no difference in mortality at 90 days with initial peritoneal drainage (34.5%) compared with initial laparotomy (35.5%). This trial strongly discouraged subsequent laparotomy after initial drainage and can be viewed as laparotomy versus "definitive" drainage rather than initial "temporizing" drainage. The second RCT comparing initial laparotomy versus peritoneal drainage enrolled 69 ELBW infants at 31 centers in 13 countries.[29] This trial was more permissive of subsequent laparotomy after initial drainage, which 74% of initial drainage patients had. Six-month survival with the initial drainage was 51.4% versus 63.6% with laparotomy ($P = .3$; risk difference 12% [95% CI: −11, 34%]). As discussed later in this section, the conclusion that there was "no significant difference" in this finding meets the traditional dichotomous views centered around a P value of less than or greater than .05 but possibly also showed clinically relevant differences in mortality rates. Importantly, neither of these early RCTs comparing laparotomy versus peritoneal drainage attempted to measure the possible impact of the preoperative diagnosis of NEC versus SIP on the treatment effect. These trials were a very important start in the investigation of our 2 current "standard" therapies but without delving into differences between NEC and SIP, it is likely that the true story is more complicated than presented.

The Necrotizing Enterocolitis Surgery Trial (NEST) is the third RCT comparing initial laparotomy versus peritoneal drainage and advances our understanding of outcomes of these therapies in infants with surgical NEC or SIP in several important ways. This trial was conducted within the robust infrastructure of the National Institute of Child Health and Human Development- Neonatal Research Network and was the first trial to meet its designated sample size, randomizing 310 ELBW infants.[30] The primary outcome was death or neurodevelopmental impairment (NDI) at 18 to 22 months corrected age, which was based on a prior observational study showing that mortality was not different in laparotomy versus drainage groups but later NDI possibly was.[31] This trial also formally assessed the possibility that the preoperative diagnosis of NEC or SIP affected the treatment effect of laparotomy versus drainage, which had not been tested previously. The NEST reported that infants with NEC do have many differences from those with a preoperative diagnosis of SIP, although some do present

Table 1
Necrotizing enterocolitis surgery trial patient characteristics by preoperative diagnosis[30]

Variable	Preop NEC (n = 95)	Preop IP (n = 213)	*P* Value
Age at initial surgery, mean (SD), d	20.93 (11.90)	7.84 (5.19)	<.001
Pneumatosis, No. (%)	34 (35.79)	11 (5.16)	<.001
Pneumoperitoneum, No. (%)	48 (50.53)	198 (92.96)	<.001
Portal vein air, No. (%)	18 (18.95)	5 (2.35)	<.001
Gasless abdomen, No. (%)	9 (9.47)	8 (3.76)	.04
Vasopressors at time of randomization, No. (%)	43 (45.26)	57 (26.76)	.001
Ventilatory support			
Conventional vent, No. (%)	56 (58.95)	151 (70.89)	.04
High frequency ventilation, No. (%)	36 (37.89)	44 (20.66)	.001
Fio_2, mean (SD)	57.71 (27.90)	39.87 (21.73)	<.001
pH, mean (SD)	7.21 (0.15)	7.25 (0.11)	.007
Birthweight, mean (SD), g	728.34 (147.05)	710.58 (132.17)	.29
Gestational Age, mean (SD), wk	25.15 (1.95)	24.88 (1.61)	.21
Weigh at initial surgery, mean (SD), g	900.37 (314.64)	706.56 (157.83)	<.001
Bluish discoloration, No. (%)	40 (42.11)	80 (37.56)	.45
Measures Prior to Randomization			
Received indomethacin before randomization, No. (%)	40 (45.45)	116 (54.98)	.13
Received postnatal steroids before randomization, No. (%)	34 (35.79)	40 (18.78)	.001
Received enteral feedings before randomization, No. (%)	65 (92.86)	120 (71.86)	<.001

Abbreviation: SD, standard deviation.

with similar features (Table 1). Although this distinction is challenging and imperfect, many pediatric surgeons use this distinction in surgical decision-making in clinical practice, typically preferring drainage for cases of SIP and laparotomy for those with NEC.[32–34] The NEST found that the preoperative diagnosis of NEC versus SIP was indeed important and significantly affected the overall treatment effect ($P = .03$). In infants with a preoperative diagnosis of NEC (n = 94), the rate of death or NDI (primary outcome) at 18 to 22 months with initial drainage was 85% compared with 69% with initial laparotomy (adjusted relative risk = 0.81 [95% CI: 0.64–1.04). The Bayesian posterior probability that laparotomy reduced the rate of death or NDI in this diagnostic group was 97%. However, in infants with a preoperative diagnosis of SIP (n = 201), the treatment effect was in the opposite direction, finding that the rate of death/NDI after initial drainage was 63% compared with 69% with laparotomy (Bayesian posterior probability with laparotomy of 18%). Stated a different way, in infants with a preoperative diagnosis of NEC, the rate of survival without impairment with laparotomy was twice that with initial drainage (31% vs 15%). The final recommendations of the NEST were that a robust effort should be made at the time of consult to distinguish NEC from SIP and that initial laparotomy is the optimal therapy for infants diagnosed with NEC. Further studies are being developed to investigate the adoption of these recommendations into practice and to elicit attitudes of pediatric surgeons, neonatologists, and parents of affected infants regarding implementation of these findings and the ethical considerations involved.

SHORT-TERM OUTCOMES

Most of the focus of larger studies evaluating outcomes with surgical NEC and SIP has appropriately been on mortality and later NDI, although other early outcomes are also important in surgical decision-making. A fairly recent systematic review reported that the overall mortality rate with surgical NEC was 34.5% and was 40.5% for ELBW infants with surgical NEC.[35] The incidence of intestinal failure, in a limited number of studies (n = 1370 infants), was between 15% and 35%. In NEST, which had a predominance of SIP infants (n = 213) compared with NEC (n = 95), the overall mortality was 29% at 18 to 22 months corrected age. The mortality with a preoperative diagnosis of NEC was 46%, consistent with prior studies and with SIP was 21%. In infants with a preoperative diagnosis of NEC, initial laparotomy resulted in a mortality rate of 40% compared with 51% with drainage. With SIP, the initial laparotomy had a mortality rate of 23% compared with 19% with initial drainage.

In NEST, infants with a preoperative diagnosis of NEC and initial laparotomy had similar duration of mechanical ventilation but shorter duration of parenteral nutrition, time to full feeds, and length of hospital stay.[30] This advantage with laparotomy was not seen with SIP infants. An important finding in NEST was that the intraoperative complication rate was higher with initial laparotomy (20%) compared with initial drainage (13%), and the most common intraoperative complication was liver hemorrhage (5% of laparotomy patients). There is likely some degree of ascertainment bias involved in intraoperative complication measurement because complications during drainage are likely more occult compared with laparotomy, nevertheless this is an important finding to consider in surgical decision-making. An outcome favoring laparotomy in NEST was that 7% of infants with a preoperative diagnosis of NEC or SIP actually had neither condition at laparotomy (2 cases of intestinal volvulus, 2 gastric perforations, and 6 other diagnoses). Also influential is the finding that 50% of initial drainage infants had a subsequent laparotomy compared with 24% after initial laparotomy (this excludes ostomy closure).

NEURODEVELOPMENTAL OUTCOMES

NDI continues to be a major problem in infants treated for surgical NEC and SIP. In the recently reported NEST, the overall rate of NDI in survivors at 18 to 22 months corrected age was 56%, which is consistent with other publications during the past decade.[30,36] NDI in this study was defined as having any of the following: moderate-to-severe cerebral palsy (CP) with Gross Motor Function Classification System level 2 or greater, Bayley-III cognitive composite score less than 85, severe bilateral visual impairment consistent with vision less than 20/200, or permanent hearing loss despite amplification that prevents communication or understanding the examiner. For infants with a preoperative diagnosis of NEC, initial laparotomy resulted in a lower rate of NDI in survivors (48%) compared with initial peritoneal drainage (68%), with a Bayesian posterior probability that laparotomy was beneficial of 89%. The rates of any NDI in infants with a preoperative diagnosis of SIP did not differ much with initial laparotomy (59%) compared with drainage (53%). Interestingly, the rate of moderate-to-severe CP did seem to be somewhat lower with initial laparotomy (16%) compared with initial drainage (24%) in infants with presumed SIP (Bayesian posterior probability of benefit with lap 89%). In infants with a preoperative diagnosis of NEC, the benefit of initial laparotomy in reducing moderate to severe CP was larger (20% with lap vs 44% with drain; Bayesian posterior probability of benefit with initial laparotomy of 94%). This protection against CP with initial laparotomy deserves further investigation to verify and determine possible mechanisms.

Although the incidence of NDI in infants with surgical NEC and SIP has not improved, the mechanisms involved are becoming clearer. A recent investigation involving an NEC mouse model and also brain tissues from infants that died with NEC (and controls) found that an underlying mechanism of NEC-related brain injury were because of gut-derived CD4+ T lymphocytes that mediated neuroinflammation, and these authors concluded that early management of intestinal inflammation in cases of NEC may improve neurologic outcomes.[37] This is a possible underlying mechanism for the lower rate of NDI in surgical NEC infants after laparotomy versus drainage reported in NEST. Other mechanisms shown to be involved include proinflammatory cytokines secondary to intestinal damage, increased growth hormone during an acute illness leading to decreased insulin-like growth factor (IGF-1) levels, changes in gut microbiome and malnutrition.[38,39]

SUMMARY

The distinction of NEC and SIP before laparotomy does need much improvement and deserves the focus of high-quality research efforts. When there is discrepancy between the preoperative and the intraoperative diagnosis of NEC or SIP, it is usually assumed that the preoperative diagnosis was incorrect. However, there has never been a study, to our knowledge, investigating the validity and consistency of the intraoperative distinction of NEC and SIP and it is likely that there is important variability in this measure. Prospective studies investigating the distinction of NEC and SIP as the primary study focus are needed but currently not available. The definitions of these conditions are also being questioned and refined over time.[40]

An interesting and unanswered question, after the publication of the 3 RCTs reviewed, is what is the level of evidence that pediatric surgeons and neonatologists should require to potentially change their practice. This question applies especially to neonatal surgery, wherein RCTs are few and far between and those that are done are typically small. For surgeons that prefer initial laparotomy for infants with a preoperative diagnosis of NEC and reserve initial drainage for those with SIP, these trial findings may serve to reinforce their practice. However, do the NEST findings warrant a change in practice for surgeons or neonatologists that may prefer initial drainage for presumed NEC infants or for those that chose between laparotomy and drainage based on patient weight or measures of acuity of illness? There is a growing call from the scientific community to avoid dichotomous conclusions based on a *P* value of less than or greater than .05 (or any other statistical metric) and the recommendation is to evaluate the point estimate of the treatment effect, the confidence interval, the quality of the conduct of the study including data integrity, the costs and risks of the therapies, and the likelihood of other trials producing more high-quality evidence.[41,42] However, many surgeons still have the dichotomous world view around the *P* value, despite often not understanding the true meaning of the *P* value. The facts that 2 of the 3 RCTs did not reach their designed sample size and that the NEST required 10 years to complete, indicate that there will not be other RCTs addressing these therapies any time soon and possibly ever. Therefore, pediatric surgeons and neonatologists will need to carefully review these data and decide for themselves how to use this in their clinical practice.

Best practices

- Make deliberate effort to distinguish NEC from SIP prior to initial operation and use the presumed preoperative diagnosis in surgical decision making.

DISCLOSURE

The authors have nothing to disclose.

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